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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/813,781	03/07/97	WEIDANZ	J 46745

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PETER F. CORLESS, ESQ.
DIKE, BROWNSTEIN, ROBERTS & CUSHMAN, LLP
130 WATER STREET
BOSTON MA 02109

EXAMINER	
LIBRET, M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/813,781	Applicant(s) Weidanz et al.
	Examiner Lubet	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Mar 30, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-59* is/are pending in the application.

Of the above, claim(s) *21-59* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Group 1600, Group 1640, Art Unit 1644.

2. Claims 1-59 are pending. Examiner acknowledges election with traverse of Group II, claims 1-8, 13-17, 18, 19 and 20. Applicant argument that it is not an undue burden for Examiner to exam all the claims. This argument is not persuasive except with regard to Group I for the reasons of record. Applicant's argument that proteins can not be made without recourse to the nucleic acids is not persuasive, since the proteins can be made chemically by chemically conjugating the recited TCR domains to bacteriophage coat proteins. **Therefore the invention of Group I and Group III claims 1-20 are under examination.**

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons set forth on the attached Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosures.

4. Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 1-18, it is unclear what the term "soluble" means. Is the term limited to solubility in aqueous medium? Is the claim language limited to a TCR molecule without any amino acid residues of transmembrane and cytoplasmic regions? Does the term encompass TCR molecules in which amino acids encoding the native transmembrane and cytoplasmic regions are replaced by other residues, IE immunoglobulin constant region genes, etc?

B. In claims 6, 11, 12, 16, 17, and 19, it is unclear what a "protein tag" is. What are the structural and functional limits of a "protein tag"?

C. In claims 1-20, it is unclear what the term "single-chain T cell receptor" means. Must the single chain T cell receptor bind form an antigen binding groove and bind the same antigen as the native TCR from which it was derived?

D. In Claim 5, it is unclear how a the fusion protein claimed in claim 2, IE a soluble fusion protein in which C-terminus of the Vα chain is covalently linked by the peptide linker sequence to the N-terminus of the Vβ chain, can be further limited to fulfill the requirements of Claim 5. Claim 2 requires that the C-terminus of the Vα chain be directly linked via a peptide linker to the N-terminus of the Vβ chain. Thus the invention recited in Claim 2 can not be modified to claim the invention claimed in claim 5. It is suggested that claim 5 be revised so that it does not depend upon claim 2. For example, "A soluble fusion protein of comprising a bacteriophage coat protein covalently linked to a single chain T cell receptor, wherein the C-terminus of the Vα chain is covalently linked to the C-α chain fragment which is covalently linked by a peptide linker sequence to the N-terminus of the Vβ chain."

E. In Claim 10, it is unclear how a the fusion protein claimed in claim 9, IE a soluble fusion comprising covalently linked in sequence (emphasis added by Examiner)(Vα-peptide linker-Vβ-BPIII protein) can be limited to fulfill the requirements of claim 10. It is suggested that claim 10 be revised so that it does not depend upon claim 9 (see 3 D supra).

F. In Claim 11, it is unclear how a the fusion protein claimed in claim 10 IE a soluble fusion comprising covalently linked in sequence (emphasis added by Examiner) recited in Claim 10, (Vα-peptide linker-Vβ-Cβ-BPIII protein) can not be modified to claim the invention claimed in claim 11.

G. In Claim 12, it is unclear how a the fusion protein claimed in claim 9 IE a soluble fusion comprising covalently linked in sequence (emphasis added by Examiner) Vα-peptide linker-Vβ-BPIII protein can t be modified to claim the invention claimed in claim 12. Thus the fusion protein of claim 12 Vα-peptide linker-Vβ- protein tag -BPIII- protein tag does fulfill the requirements of Claim 9 since the elements recited in claim 9 are linked in sequence and thus must not have any intervening sequences.

H. In Claim 16, it is unclear how a the fusion protein claimed in claim 13 IE a soluble fusion comprising covalently linked in sequence (emphasis added by Examiner) Vα-peptide linker-Vβ-VIII protein can be modified to claim the invention claimed in claim 16 because the fusion protein of claim 16 Vα-peptide linker-Vβ- protein tag -BPVIII- protein tag does fulfill the requirements of Claim 13 since the elements recited in claim 13 are linked in sequence and thus must not have any intervening sequences.

I. In Claim 17, it is unclear how a the fusion protein claimed in claims 14 or 15 IE a soluble fusion comprising covalently linked **in sequence** (emphasis added by Examiner) Vα-peptide linker-- linker-Vβ-Cβ- VIII protein or Vα-Cα-peptide linker-Vβ- Cβ-VIII protein can be modified to claim the invention claimed in claim 17. Thus the fusion protein of claim 17 Vα-peptide linker-Vβ- protein tag -BPVIII- protein tag does fulfill the requirements of Claims 14 since the elements recited in claim 14 are linked in sequence and thus must not have any intervening sequences.

J. In claims 9 and 12 there it is unclear if the N-terminus of the VIII protein must be covalently linked to the C-terminus of the Vβ chain.

K. Claim 9 contains a typographical error. There are two "3)" recited in the claim. The second "3)" should be "4)".

L. In claim 20, it is unclear what the term "humanized" means. Does the term encompass linking of any human derived sequence, IE IgG constant region genes derived from human antibody to the single chain TCR comprising Vα and Vβ domains. Must the "humanized" sequences must be attached to both Vα and Vβ domains? Must the "humanized" sequences be attached to C-terminus?

M. The claims recites TCR Vα and Vβ chains. TCR beta chain comprises V regions and C regions (see Choi et al, US Patent 5,616,472, column 2, lines 15-43, in particular). It is unclear what amino acid residues are encompassed by the claim language. Does the V chain include VDJ regions of beta chains and VJ of alpha chains ? Applicant is required to point out the metes and

bounds of the term. It is suggested that the claims be amended to refer "V regions" and "C regions" and not "V chains" and "C regions" and point out which amino acid residues of TCR are encompassed by the claim language.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas US Patent 5,759,817 (issued June 2, 1998, priority to Jun. 27, 1992) and Onda et al. (Molecular Immunology 32:1387, 1995) in view of Schodin et al. (Molecular Immunology 33:819, 1996), Novotny et al.(PNAS 88:8646, 1991), W0 96/18105 (issued June 13, 1996), Ward (Scand. J. Immunol. 34:215, 1991) or Kappler et al. (PNAS 91:6462; 1991).

A. Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C)

region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Thus Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains.

Onda et al .disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used

to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular).

B. Barbas and Onda et al. do not teach a soluble fusion protein which comprises bacteriophage coat protein covalently linked to a single chain TCR which comprises V-α domain linked via a peptide linker to Vβ domain.

However, Schodin et al. teaches single chain T cell receptors comprising V-α domain linked via a peptide linker to Vβ domain linked to thioredoxin and that such a fusion protein allows for increased yields of soluble TCR (see abstract and page 819-820, in particular). In the single chain TCR heterodimer taught by Schodin et al. the carboxyl terminus of Vβ domain is linked to the amino terminus of Vα domain via a peptide linker that is 25 amino acids long (see Figure 1, in particular). The claim language of Claim 7 reads upon the peptide linker taught by Schodin et al. because of the use of the term "from approximately". Schodin et al. teach that the TCR may be derived from a cytotoxic T lymphocyte clone (see page 820, first paragraph, in particular). Schodin et al. further teach that the single chain TCR may be comprise a protein tag such as histidine (see Figure 1) and that the majority of TCR-thioredoxin fusion protein fold into three dimensional structure which is recognized by clonotypic antibody and that the fusion protein binds to peptide/MHC ligand (see page 826, second paragraph, in particular). Schodin et al. further teach that modeling of TCR based on its primary structure has suggested the tertiary structure is similar to that of immunoglobulin (see page 819, in particular).

Novotny et al. teach a soluble single chain T cell receptor comprising Vβ domain linked to Vα domain via a 15-20 amino acid linker (see Figure 1, and page 8048, in particular). Novotny et al. further teach that the single chain TCR protein binds its ligand (FITC) specifically (see page 8650, in particular).

WO 06/18105 teaches single chain T cell receptor which specifically binds to peptide ligand (see abstract). WO 96/18105 further teaches one embodiment of the single chain TCR in which C-terminus of Vα domain is linked to N-terminus of Vβ chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the Vβ chain is linked to the beta chain constant domain (see page 3 and Figure 1, in particular). In one embodiment the C terminus of Vβ chain is linked to a alkaline phosphatase (PI) protein tag (see Figure 1, in particular). WO 96/18105 also teaches that the order of the domains within the single chain TCR is interchangeable (see page 5, in particular). WO 96/18105 also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. WO 96/18105 also teach that a preferred embodiments of linkers are composed of amino acids which tend to increase solubility in aqueous solution (see page 8, lines 1-25, in particular).

The W0 96/18105 further teaches that the single chain TCR may be derivatized by conjugation of group which does not alter the binding characteristics of the single chain TCR (see page 9, lines 2-20, in particular).

Ward teaches single chain TCR comprising Vα domain linked to Vβ domain with a protein tag comprising HIS_6 can be purified in yields of approximately 1 to 2 mg/liter (see Figure 1 and page 885, in particular). Ward also teaches that TCR variable regions contain a high proportion of β-pleated sheet structures that resemble immunoglobulin Fv and Fab fragments in structure (see page 888, second paragraph, in particular).

Kappler et al. teach soluble single chain TCR comprising Vα- Cα- linker -Vβ-Cβ in which the Cα and Cβ domains are truncated just prior to the portion encoding the transmembrane region (see Figure 1, abstract , in particular)

Therefore, it would have been *prima facie* obvious to one with skill in the art at the time of the invention to substitute to single chain TCR fusion molecules taught by Schodin et al., Novotny et al., WO 96/18105, Ward or Kappler et al. for the TCR residues of the TCR-bacteriophage coat protein soluble fusion protein taught by Barbas and Onda et al. with the expectation that the fusion protein would be produced in large quantities and used to elicit anti-TCR antibodies or used to study specific binding interactions of the TCR chain to antigenic ligands as taught by Onda et al.

7. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas US Patent 5,759,817 (issued June 2, 1998, priority to Jun. 27, 1992) and Onda et al. (Molecular Immunology 32:1387, 1995) in view of Schodin et al. (Molecular Immunology 33:819, 1996), , Novotny et al.(PNAS 88:8646, 1991), W0 96/18105 (issued June 13, 1996), Ward (Scand. J.

Immunol. 34:215, 1991) or Kappler et al. (PNAS 91:6462, 1991) and further in view of Choi et al. US Patent 5,616,472 (issued April 1, 1997, priority to Aug. 9, 1990).

A. Barbas US Patent 5,759,817, Onda et al., Schodin et al., Novotny et al., W0 96/18105, Ward, and Kappler et al (PNAS 91:6462, 1991) have been discussed supra. Thus these references in combination disclose soluble fusion single chain TCR-bacteriophage coat proteins claimed in claims 1-19 but do not disclose the humanized TCR-bacteriophage fusion protein claimed in claim 20.

However, Choi et al. disclose humanized, chimeric T cell receptors which comprise one human element and the rest of the elements are non-human animal species such as a mouse (see abstract, column 6, line 10 through column 7, line 35, in particular) and that such chimeric proteins may be used to elicit monoclonal antibodies specific for human portion of the chimeric protein.

Therefore, one with skill in the art at the time of the invention would be motivated to modify the single-chain TCR-bacteriophage soluble fusion protein taught by the prior art cited supra, by humanizing at least one of the domains of the TCR portion of the fusion protein as taught by Choi et al. with the expectation that the resulting humanized single chain TCR-bacteriophage could be used to elicit antibody to TCR.

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

applicant may become aware in the specification.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet

June 17, 1998

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800